REMARKS

Examiner's Rejections and Objections

The foregoing Amendment and remarks which follow are responsive to the final Office Action mailed December 2, 2002. In that Office Action, the Examiner indicated that Claims 16-52 were withdrawn from consideration as being directed to a non-elected invention. The Examiner constructively elected Claims 1-15 for consideration as they were originally presented for prosecution on the merits. In this regard, Applicant confirms such election by the Examiner by cancelling out Claims 16-52 herein and maintaining the prosecution of Claims 1-15. Thus, it is respectfully submitted that any issue as to restriction has now been overcome.

Further in that Office Action, the Examiner objected Applicant's amendment of September 23, 220 under 35 U.S.C. §132 because it introduces new matter into the disclosure. Essentially, the Examiner required Applicant to cancel the alleged new matter from the disclosure. In order to expedite the prosecution of the subject patent application, Applicant has clarified its disclosure back to the form it was originally in prior to the last filed amendment.

The Examiner rejected Claim 11 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as its invention. As such, Applicant has amended Claim 11 in a

manner as to resolve the pending §112 rejection currently raised by the Examiner.

On a more substantive note, the Examiner rejected Claims 1, 2 and 5-10 under 35 U.S.C. §102(b) as being anticipated by the Akimoto et al. reference ("Akimoto"). Moreover, Claims 1, 3-7, 9 and 10 were rejected under 35 U.S.C. §102(b) as being anticipated by the Derwent English abstract of Japanese Patent Application No. 05/178,793 ("'793 abstract").

Additionally, the Examiner rejected Claims 1, 3, 4, 6, 7 and 11-15 under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as being obvious over Akimoto. Lastly, Claims 1, 2, 6, 7 and 11-15 were rejected under 35 U.S.C. §103(a) as being unpatentable over '793 abstract.

As will be demonstrated below, Applicant respectfully submits that the present invention, as reflected in the amended independent claims, should not be anticipated or rendered obvious by Akimoto and/or '793 abstract.

Amended Independent Claims 1 and 12

Applicant has again amended independent Claims 1 and 12 to further clarify its invention in accordance with the phone conversation of April 22, 2003 with the Examiner. As expressed in that phone conversation, these claims now incorporate the heart of the subject matter of dependent Claim 11 to recite a composition

containing Asiasari Radix extracts which are: (1) subjected to multiple pH adjustments with an acid and a base; (2) extracted with a chlorinated aliphatic solvent; and (3) fractionated with a methanol for the ultimate purpose of improving memory and protecting brain cells against damage caused by excitatory amino acids and oxidative stresses. As further expressed in that conversation, Applicant includes herewith the Declaration of Dr. Sung-Jin Kim, the inventor of the subject invention, to affirmatively support the notion that the resulting extracts are significantly distinguishable from the ones disclosed in Akimoto or the '793 abstract.

In particular, the composition of the present invention is specifically manufactured to be utilized by normal subjects without any particular diseases or conditions for improving their memories and protecting their brain cells against any potential damage that may be caused by excitatory amino acids and oxidative stresses. In other words, the present composition is primarily intended for healthy individuals who wish to optimize their cognizant capabilities through daily intake of the composition. It should be well noted that such composition should be deemed as an enhancer, and not a remedy aimed at curing or alleviating any specified disease or condition of a human body such as hypertension or inflammation.

In order to derive the composition of the present invention,

a naturally-occurring plant Asiasari Radix is used as an essential ingredient thereof. However, it should be recognized that this plant is specially prepared and integrated into the present composition. More specifically, among other preparatory procedures, the Asiasari Radix is subjected to multiple pH adjustments with an acid (to pH 2-4) and a base (to pH 9-12). It is also distinctively extracted through the use of a chlorinated aliphatic solvent such as chloroform and fractionated with a methanol. By this specified extraction process, an Asiasari Radix composition for memory improvement and brain cell protection can be satisfactorily created.

Applicant submits that, as understood, Akimoto does not teach or suggest such composition containing Asiasari Radix which is: subjected to multiple pH adjustments with an acid and a base; (2) extracted with a chlorinated aliphatic solvent; and (3) fractionated with a methanol for the ultimate purpose of improving memory and protecting brain cells against damage caused by excitatory amino acids and oxidative stresses in a normal healthy subject. Rather, Akimoto is understood to disclose a derivatized sesamin and/or episesamin compound which is specifically adapted at remedying "hypertension or medical symptoms caused thereby." (Column 2, lines 40-41). Simply put, Applicant submits that Akimoto's compound is essentially formed to be an answer to a specific condition of hypertension.

Furthermore, it is believed that Akimoto's compound does not use all, or even most, of the above-noted procedures of the present invention for extracting its required sesamin and/or episesamin. As understood by Applicant, Akimoto utilizes "organic solvents that are essentially immiscible with sesame oil and are able to extract and dissolve the derivative of the present invention." (Column 4, lines 48-50). Specific examples of such organic solvents include "acetone, methyl ethyl ketone, diethyl ketone, methanol and ethanol." (Column 4, lines 51-52). Hence, it is respectfully submitted that the resulting product of Akimoto is sufficiently distinguishable from the extracts of the present invention. See, Declaration of Sung-Jin Kim, Ph.D.

Likewise, the '793 abstract is not also understood to disclose a composition containing Asiasari Radix which is: subjected to multiple pH adjustments with an acid and a base; (2) extracted with a chlorinated aliphatic solvent; and (3) fractionated with a methanol for the ultimate purpose of improving memory and protecting brain cells against damage caused by excitatory amino acids and oxidative stresses in a normal healthy subject. Instead, Applicant understands the '793 abstract to disclose a formula which is remedial in nature as it is specifically described as being "useful as anti-allergic or anti-inflammatory agents." (Page 1, paragraph 11). Based upon such description, Applicant respectfully submits that '793 abstract's formula is primarily a remedy for a

specific bodily condition or disease of allergy or inflammation.

In addition, the formula of '793 abstract is not understood to utilize all, or even most, of the above-noted procedures of the present invention during its production process. Rather, it is understood to resort to different procedures such as performing extraction "with water, MeOH, EtOH, acetone or EtOAc." (Page 1, paragraph 10). To reinforce such notion, Applicant points to '793 abstract's only described experiment which its formula was "extracted with 96L MeOH." (Page 1, paragraph 12). Thus, it is respectfully believed that the resulting product of the '793 application is patentably distinguishable from the extracts of the present invention. See, Declaration of Sung-Jin Kim, Ph.D.

In summary, Applicant submits that the prior art fails to teach or suggest the specified composition of the present invention geared toward healthy individuals for memory improvement and brain cell protection, and it would be unobvious to one of ordinary skill in the art to develop such an invention. Applicant believes that Akimoto is primarily used for remedying a specific disease or condition of hypertension, while '793 abstract is directed to remedying a different specific disease or condition of allergy or inflammation. Moreover, Applicant further submits that both of the prior art references fail to disclose the use of such specific procedures noted in the present invention during their respective extraction processes. Simply put, it would be unobvious to one of

ordinary skill in the art to develop the above-illustrated composition of the present invention in view of the above two references with purposes that are not relatable to each other, or to the present invention for that matter.

Applicant respectfully submits that amended independent Claims 1 and 12 are novel and unobvious in view of the cited prior art, and thus allowable. Insofar as the amended independent Claim 1 and are is believed to be allowable, their respective dependent claims are also believed to be allowable.

For the foregoing reasons, Applicant respectfully requests reconsideration of the rejections under 35 U.S.C. §§ 102(b) and 103(a).

Request for Allowance

On the basis of the foregoing, Applicant respectfully submits that all the stated grounds of rejections have been overcome, and that all of the pending claims are now in condition for allowance. An early Notice of Allowance is therefore respectfully requested.

Attached hereto is a marked-up version of the clarifications made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." An early Notice of Allowance is therefore respectfully requested.

Should the Examiner have any suggestions for expediting allowance of the application, the Examiner is invited to contact

Applicant's representative at the telephone number listed below.

Respectfully submitted,

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Version With Markings To Show Changes Made

IN THE SPECIFICATION:

Please replace paragraph [0009] with the following rewritten paragraph:

--Interesting hypothesis has been proposed that sporadic Alzheimer disease might be the brain type of non-insulin dependent diabetes mellitus (Hoyer, S. Is sporadic Alzheimer disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis. J. Neural Transm. 105, 415-422, 1998). It has been suggested that intracerebroventricular insulin enhances memory in a passive-avoidance task [Park, C. P., Seeley, R. J., Craft, S. and Woods S. C. (2000) Intracerebroventricular insulin enhances memory in a passive avoidance task. Physiol. Behav. 68, 509-514]. Insulin receptor density and tyrosine kinase activity in the sporadic Alzheimer's disease (SDAT) was known to be significantly decreased [Frolich, L., Blum-degen, D., Bernstein, H. G., Engelsberger, S., Humrich, J., Laufer, S., Muschner, D., Thalheimer, A., Turk, A., Hoyer, S., Zochling, R., Boissl, K. W., Jellinger, K., and Piederer, P. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J. Neural Transm. 105, 423-438, 1998]. Interestingly, tyrosine phosphorylation of the hippocampal insulin receptor has been shown to play an essential role in

spatial memory formation [Zhao, W., Chen, H., Xu, H., Moore, E., Meiri, N., Quon, M. J., Alkon, D. L. (1999) Brain insulin receptors and spatial memory. J. Biol. Chem. 274, 34893-34902, 1999]. Taken together, insulin receptor activators ccould be used for memory enhancement in addition to cholinesterase inhibitors.--

Please delete paragraph [0010] which is after paragraph [0009] as follows:

[Recently, it has been found that ERK (Extracellular signal-Regulated Kinase or MAPK) I and II, which are important downstream signaling mediators of the insulin receptor, are implicated in memory and learning [Thiels, E, Klann, E. Extracellular signal-regulated kinase, synaptic plasticity, and memory. Rev. Neurosci. 12, 327-345, 2001; Sweat J.D. The neuronal MAP kinase cascade: a biochemical signal integration system subserving synaptic plasticity and memore. J. Neurochem. 76, 1-10, 2001]. It has been also demonstrated that rats subjected to avoidance learning showed significant and specific increases in the activated forms of ERK I and II in the rat hippocampus [Cammarota, M., Bevilaqua, L.R.M., Ardenghi, P., Paratcha, G., de Stein, M.L., Iaqueirdo, I., Medina, J.H. Learning-associated activation of nuclear MAPK, CREB and Elk-1, along with Fos production, in the rat

hoppocampus after a one-trial avoidance learning; abolition by NMDA receptor blockade. Mol. Brain Res. 76, 36-46, 2000]. Taken together, insulin receptor and ERK I/II activators could be used for memory enhancement in addition to cholinesterase inhibitors.]

Please replace Paragraph [0072] with the following rewritten paragraph:

--The test was basically performed according to the step-through method described by Jarvik and Kopp [Jarvik, M. E. and Kopp, R. An improved one-trial passive avoidance learning situation. Pschol. Rep. 21, 221-224, 1967]. The Gemini Avoidance System (SD Instruments) was used for this experiments. The apparatus consists of a two-compartment acrylic box with a lightened compartment connected to a darkened one by an automatic guillotine door. Mice were placed in the lighted box for 300 sec. Then, the guillotine door was open. Mice, as soon as they entered the dark compartment, received a punishing electrical shock (0.3 mA, 1 sec). The latency times for entering the dark compartment were measured in the training test and after 24 hr in the retention test. The maximum entry latency allowed in the retention session was 500 sec. [Fraction 1, 2 or 4 (10 mg/kg/day, P.O.) was administered once a day for three days and t sted for the

passive avoidance test.]--

Please replace paragraph [0078] with the following rewritten paragraph:

--Male Sprague Dawley rats were decapitated [after 60 min. following the administration of AR extracts] and subjected to the isolation of hippocampus on 4C.. Hippocampal homogenates were prepared as described earlier with some modifications [Zhao, W., Chen, H., Xu, H., Moore, E., Meiri, N., Quon, M. J., Alkon, D. L., Insulin receptors and spatial memory. J. Biol. Chem. 274, 34893-34902, 1999]. The isolated hippocampus was resuspended with buffer A containing 50 mM Tris HCl, pH 7.4, 1 mM EDTA, 1 mM EGTA, 150 mM NaCl, 1% Triton X-100, 0.5 mM PMSF, 1 mM Na_3VO_4, 1ug/ml of leupeptin and aprotinin and subjected to homogenization with a Potter-Elvehjem homogenizer. The lysates were then spun at [10,000 x g for 20 min] 1,000 x g fo 5 min and the supernatant were subjected to protein assay and saved at 70°C.--

Please replace paragraph [0083] with the following rewritten paragraph:

--Equal amount of hippocampal proteins were applied to SDS polyacrylamide gel. Electrotransfer of proteins from the gels to nitrocellulose paper (Schleicher & Schuell) was carried out

for 1 hr at 100 V (constant) as described by Towbin et al. [Towbin H., Staehelin, J., Gordon, J. Electric transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. Proc. Natl. Acad. Aci. USA 76, 4350-4354, 1979]. The filter papers were preincubated for 1 hr at 23 C with PBS containing 0.1% Tween 20 and 3% bovine serum albumin and washed with PBS containing 0.1% Tween 20 three times for 10 min each. The blots were probed with pTyr [or pERK] antibodies for 1 hr at 23 C. The blots were then incubated with HRP-conjugated anti-rabbit IgG for 30 min and washed with PBS containing Tween 20 five times for 10 min each. The detection of immobilized specific antigens was carried out by ECL (NEN). --

Please replace paragraph [0088] with the following rewritten paragraph:

--Male SD rats were dosed p.o. with vehicle or fractions of AR extract. The rats were decapitated after [60] 90 min, brains rapidly removed, hippocampus and corpora striata dissected free, weighed and homogenized as described above. Cholinesterase activity was measured as described by Ellman et al [Ellman, G. L., Courtney, K. D., Andres, V., Featherstone, R. M. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Pharmacol. 7, 88-

95.1961]. Briefly, 3 ml of buffer I (100 mM phosphate, pH 8.0), 0.2 ml of 75 mM acetylthiocholine iodide and 0.1 ml of buffered Ellman's reagent (DTNB 10 mM, NaHCO3 15 mM) were mixed and allowed to incubate for 10 min at 25°C. Then, 20 ml of enzyme sample was added and absorbance was measured at 30 sec intervals. The percent inhibition was calculated by comparison with the enzyme activity of the vehicle control group.--

IN THE CLAIMS:

Please cancel Claims 16-52 without prejudice.

Please amend the following claims:

1. (Twice Amended) A composition containing Asiasari Radix extracts subjected to multiple pH adjustments with an acid and a base, the extracts being extracted with a chlorinated aliphatic solvent and further fractionated with a methanol, the extracts having at least two therapeutically effective agents therein for improving memory and protecting brain cells against damage caused by excitatory amino acids and oxidative stresses.

11. (Twice Amended) The composition of Claim 1, wherein said the Asiasari Radix extracts are obtained by the following sequential fractionation procedure:

a) extracting Asiasari Radix with a lower alcohol mixed with water;

b) adjusting the pH to 2-4 with the acid;

c) extract the solution in step b) with an equal volume of chloroform;

d) isolating a chloroform insoluble fraction;

e) adjusting the pH of the [solution] fraction in step d) to 9-12 with NH4OH;

f) subjecting the [solution] fraction in step d) to an extraction with equal volume of a chloroform:methanol mixed solvent; and

g) isolating and extracting a methanol insoluble fraction from step f) and fractionating the same with the methanol to obtain the Asiasari Radix extracts which are methanol soluble.

12. (Twice Amended) A composition for improving memory and protecting brain cells containing a chloroform fraction of Asiasari Radix extracts obtained by the following sequential fractionation procedure: subjecting Asiasari Radix to extraction with a lower alcohol having between 1 carbon atom and 4 carbon atoms or organic solvent, the resulting Asiasari Radix extract being solublized in a methanol:water mixed solvent having a pH adjusted to 2-4 with an acid and to 9-12 with a base, the extracts being subjected to extraction with equal volume of a chlorinated aliphatic solvent such as chloroform to obtain a chloroform fraction of Asiasari Radix extracts for improving memory and protecting brain cells against damage caused by excitatory amino

acids and oxidative stresses.